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WO 00/43395 A1

(54) Title: SUBSTITUTED PORPHYRINS

(57) Abstract: The present invention relates, in general, to a method of modulating physiological and pathological processes and, in particular, to a method of modulating cellular levels of oxidants and thereby processes in which such oxidants are a participant. The invention also relates to compounds and compositions suitable for use in such methods.

SUBSTITUTED PORPHYRINS

TECHNICAL FIELD

The present invention relates, in general, to a method of modulating physiological and pathological processes and, in particular, to a method of modulating cellular levels of oxidants and thereby processes in which such oxidants are a participant. The invention also relates to compounds and compositions suitable for use in such methods.

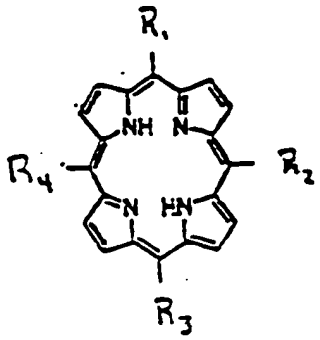
BACKGROUND

Oxidants are produced as part of the normal metabolism of all cells but also are an important component of the pathogenesis of many disease processes. Reactive oxygen species, for example, are critical elements of the pathogenesis of diseases of the lung, the cardiovascular system, the gastrointestinal system, the central nervous system and skeletal muscle. Oxygen free radicals also play a role in modulating the effects of nitric oxide (NO·). In this context, they contribute to the pathogenesis of vascular disorders. inflammatory diseases and the aging process.

A critical balance of defensive enzymes against oxidants is required to maintain normal cell and organ function. Superoxide dismutases (SODs) are a family of metalloenzymes that catalyze the intra- and extracellular conversion of O_2^- into H_2O_2 plus O_2, and represent the first line of defense against the detrimental effects of superoxide radicals. Mammals produce three distinct SODs. One is a dimeric copper- and zinc-containing enzyme (CuZn SOD) found in the cytosol of all cells. A second is a tetrameric manganese-containing SOD (Mn SOD) found within mitochondria, and the third is a tetrameric, glycosylated, copper- and

WHAT IS CLAIMED IS:

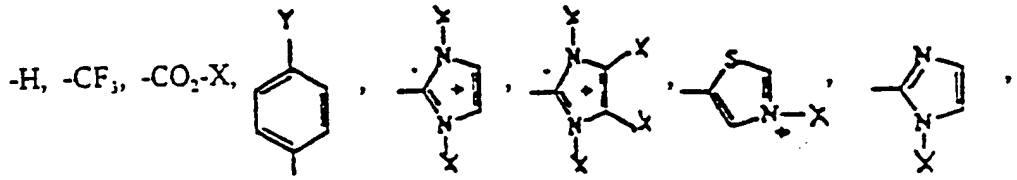
1. A compound of formula

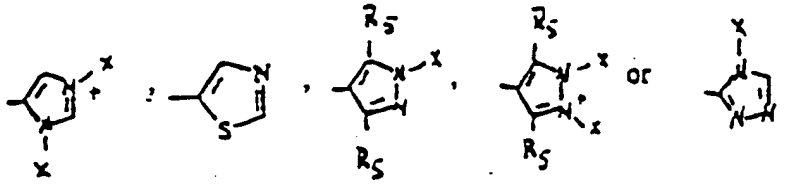


or pharmaceutically acceptable salt thereof,

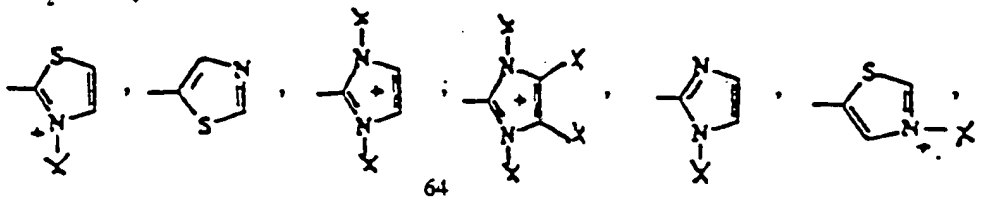
wherein

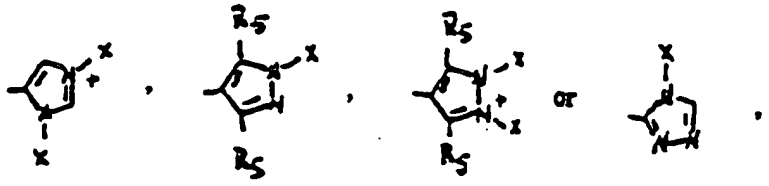
R_1 and R_3 are the same and are:





R_2 and R_4 are the same and are :

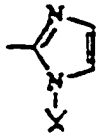




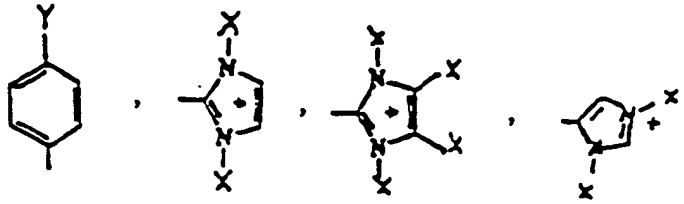
Y is halogen or $-CO_2X$, and

X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl.

wherein when R_1 and R_3 are -H, R_2 and R_4 are not  . or

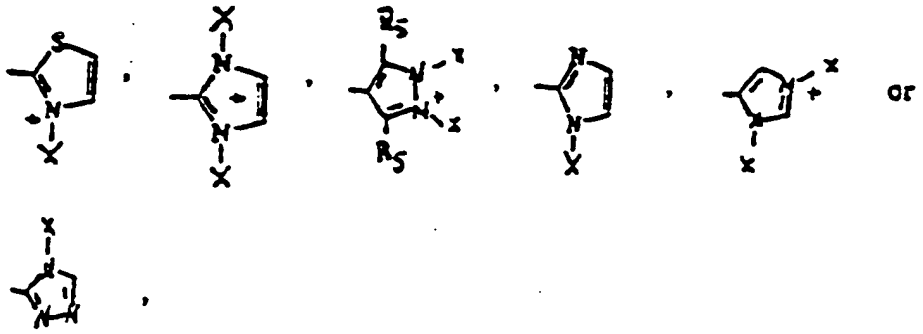
when R_1 and R_3 are -H, and R_2 and R_4 are  , said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt or nickel.

2. The compound according to claim 1 wherein R_1 and R_3 are the same and are:

-H, CF_3, $-CO_2-X$, 

or  ,

R_2 and R_4 are the same and are :



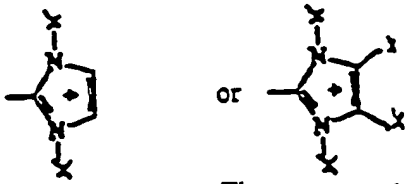
Y is -F or $-CO_2X$, and

X is the same or different and is a C_{1-4} alkyl and each R_5 is the same or different and is H or C_{1-4} alkyl.

3. The compound according to claim 2 wherein X is methyl or ethyl.

4. The compound according to claim 1 wherein R_1, R_2, R_3 and R_4 are the same.

5. The compound according to claim 1 wherein R_1, R_2, R_3 and R_4 are



o. The compound according to claim 5 wherein X is methyl or ethyl.

7. The compound according to claim 5 wherein R_1, R_2, R_3 and R_4 are the same.

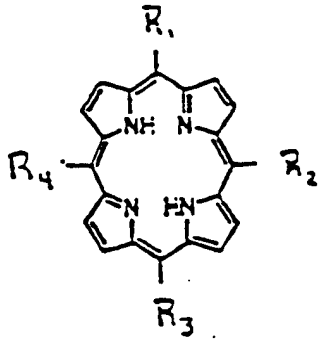
8. The compound according to claim 7 wherein R_1, R_2, R_3 and R_4 are

.

9. The compound according to claim 1 wherein said compound is complexed with a metal selected from the group consisting of zinc, iron, nickel, cobalt, copper, manganese.

10. The compound according to claim 9 wherein said compound is complexed with manganese.

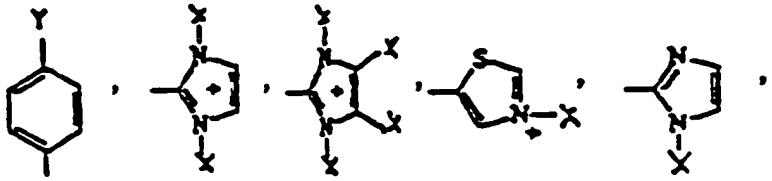
11. A method of protecting cells from oxidant- induced toxicity comprising contacting said cells with a protective amount of a compound of formula

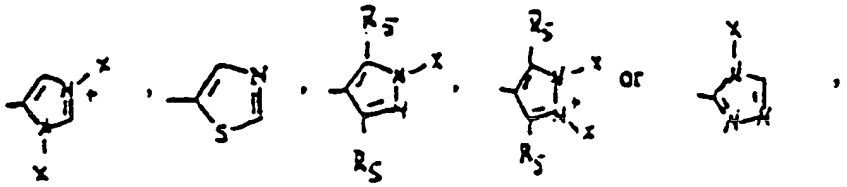


or pharmaceutically acceptable salt thereof,

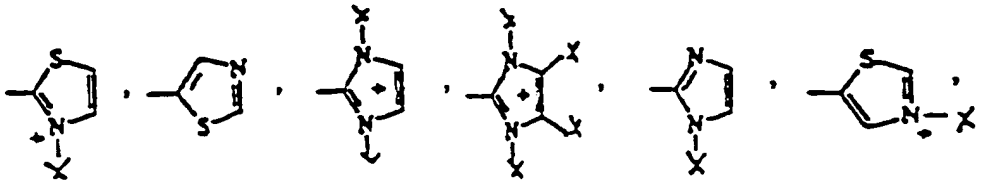
wherein

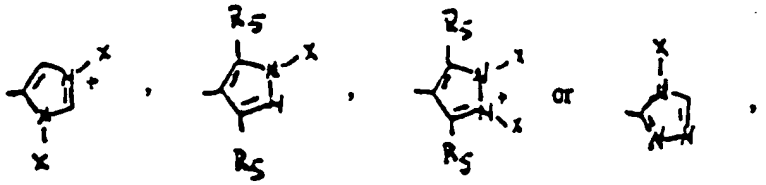
R_1 and R_3 are the same and are:

-H, -CF_3, -CO_2-X, 



R_2 and R_4 are the same and are :





Y is halogen or -CO_2X, and

X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said protection is effected.

12. The method according to claim 11 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

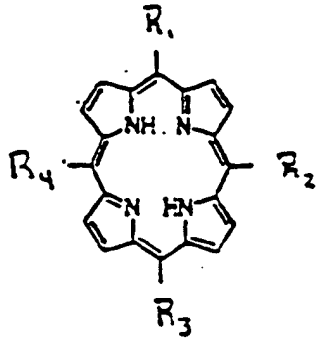
13. The method according to claim 12 wherein said metal is manganese.

14. The method according to claim 11 wherein said cells are mammalian cells.

15. The method according to claim 14 wherein said cells are cells of an isolated organ.

16. The method according to claim 14 wherein said cells are cells of an organ transplant.

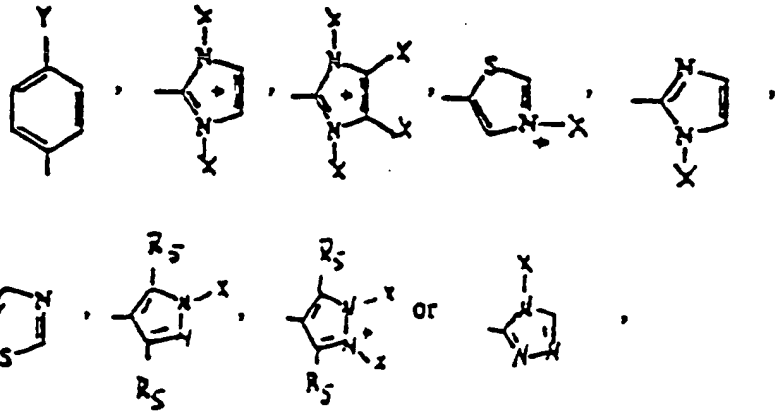
17. A method of treating a patient suffering from a condition that results from or that is exacerbated by oxidant-induced toxicity comprising administering to said patient an effective amount of a compound of formula



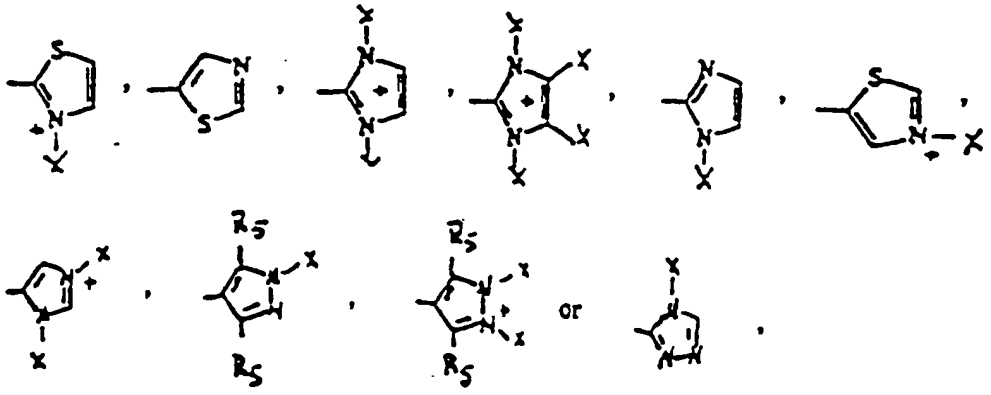
or pharmaceutically acceptable salt thereof,

wherein

R_1 and R_3 are the same and are:

-H, -CF_3, -CO_2-X, 

R_2 and R_4 are the same and are :



Y is halogen or $-CO_2X$, and

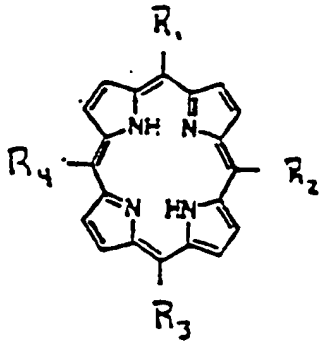
X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said treatment is effected.

18. The method according to claim 17 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

19. The method according to claim 18 wherein said compound is complexed with manganese.

20. A method of treating a pathological condition of a patient resulting from degradation of NO· or a biologically active form thereof, comprising administering to said patient an effective amount of a compound of formula



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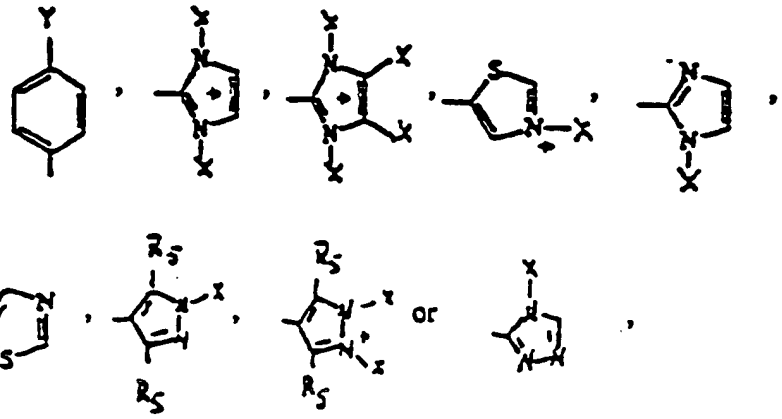
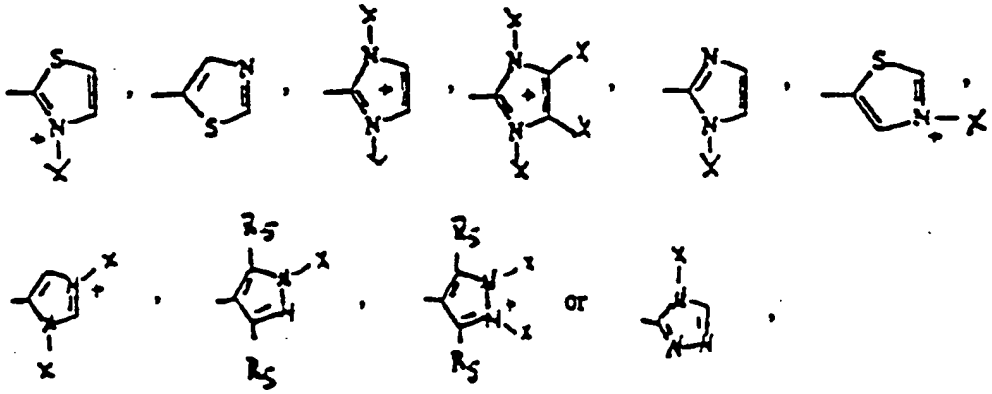
or pharmaceutically acceptable salt thereof,

wherein

R_1 and R_3 are the same and are:

-H, -CF_3, -CO_2-X, 

R_2 and R_4 are the same and are :



Y is halogen or -CO_2X, and

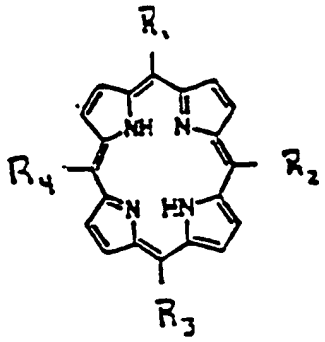
X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said treatment is effected.

21. The method according to claim 20 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

22. The method according to claim 21 wherein said compound is complexed with manganese.

23. A method of treating a patient for an inflammatory disease comprising administering to said patient an effective amount of a compound of formula



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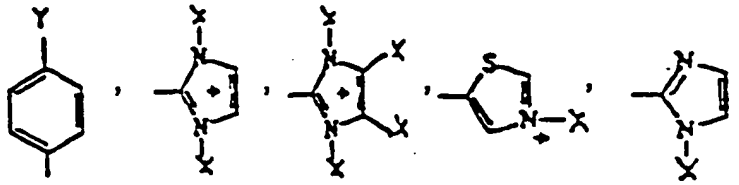
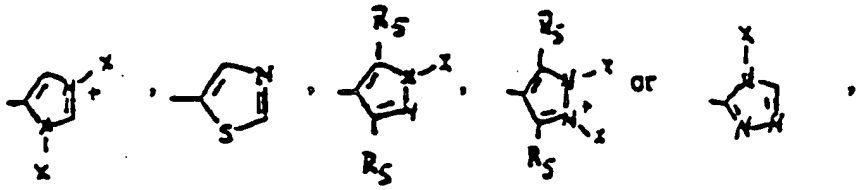
or pharmaceutically acceptable salt thereof.

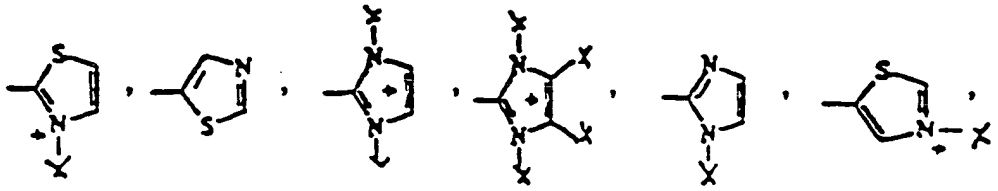
wherein

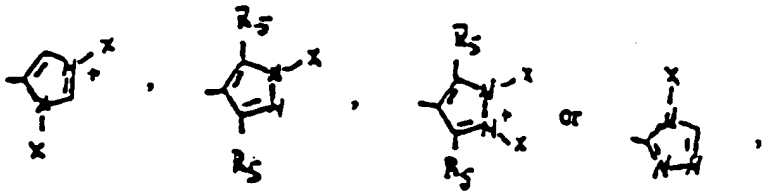
R_1 and R_3 are the same and are:

-H, -CF_3, -CO_2-X, 



R_2 and R_4 are the same and are :





Y is halogen or $-CO_2X$, and

X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said treatment is effected.

24. The method according to claim 23 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

25. The method according to claim 24 wherein said compound is complexed with manganese.

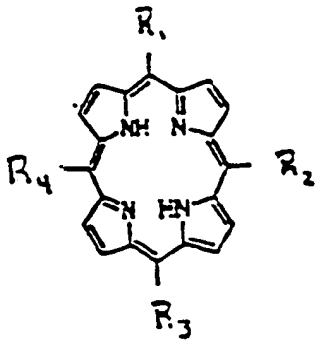
26. The method according to claim 23 wherein said inflammatory disease is an inflammatory lung disease.

27. The method according to claim 26 wherein said inflammatory lung disease is bronchopulmonary disease.

28. The method according to claim 26 wherein said inflammatory lung disease is asthma.

29. The method according to claim 26 wherein said inflammatory lung disease is pulmonary fibrosis.

30. A method of treating a patient for an ischemic reperfusion injury comprising administering to said patient an effective amount of a compound of formula



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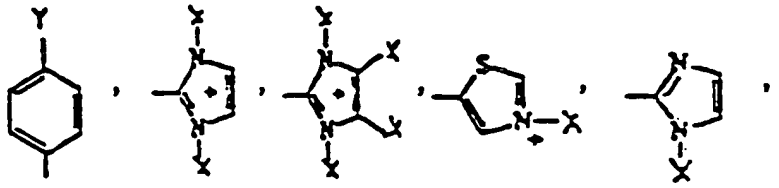
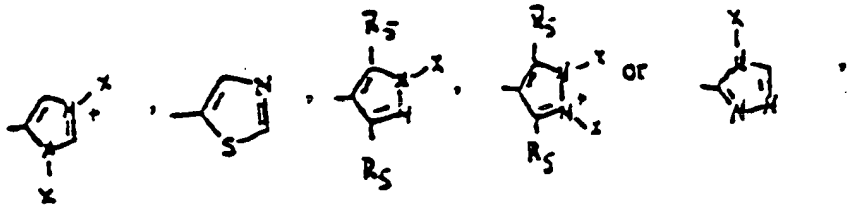
or pharmaceutically acceptable salt thereof,

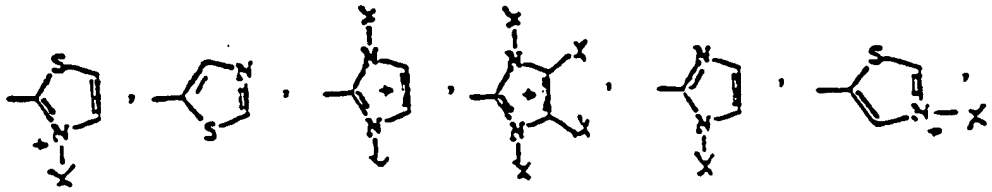
wherein

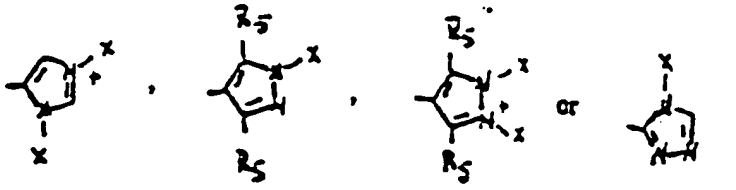
R_1 and R_3 are the same and are:

-H, -CF_3, -CO_2-X, 



R_2 and R_4 are the same and are :





Y is halogen or -CO_2X, and

X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said treatment is effected.

31. The method according to claim 30 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

32. The method according to claim 31 wherein said compound is complexed with manganese.

33. The method according to claim 30 wherein said ischemic reperfusion injury results from a stroke.